From the Southern Association for Vascular Surgery

Natural history of limbs with arterial insufficiency and chronic ulceration treated without revascularization

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Objectives: **The natural history of limbs affected by ischemic ulceration is poorly understood. In this report, we describe the outcome of limbs with stable chronic leg ulcers and arterial insufficiency that were treated with wound-healing techniques in patients who were not candidates for revascularization.**

Methods: **A prospectively maintained database of limb ulcers treated at a comprehensive wound center was used to identify patients with arterial insufficiency, defined as an ankle-brachial index (ABI) <0.7 or a toe pressure <50 mm Hg. Patients were treated without revascularization when medical comorbidity or anatomic considerations did not allow revascularization with acceptable risk. Ulcers were treated with a protocol emphasizing pressure relief, débridement, infection control, and moist wound healing. Risk factors analyzed for their affect on healing and amputation risk included age, gender, diabetes mellitus, chronic renal insufficiency (serum creatinine > 2.5 mg/dL), severity of ischemia measured by ABI or toe pressure, wound grade, wound size, and wound location.**

Results: **Between January 1999 and March 2005, 142 patients with 169 limbs having arterial insufficiency and full-thickness ulceration were treated without revascularization. Mean patient age was 70.8 ± 4.5. Diabetes mellitus was present in 70.4% of limbs and chronic renal insufficiency in 27.8%. Toe amputations or other foot-sparing procedures were performed in 28% of limbs. Overall, limb loss occurred in 37 patients. By life-table analysis, 19% of limbs required amputation ≤6 months of initial treatment and 23% at 12 months. Complete wound closure was achieved in 25% by 6 months and in 52% by 12 months. Statistical analysis showed a correlation between ABI and the risk of limb loss. In patients with an ABI <0.5, 28% and 34% of limbs experienced limb loss at 6 and 12 months, respectively, compared with 10% and 15% of limbs in patients with an ABI >0.5 (*P* = .01). The only risk factor associated with wound closure was initial wound size (*P* < .005).**

Conclusions: **Limb salvage can be achieved in most patients with arterial insufficiency and uncomplicated chronic nonhealing limb ulcers using a program of wound management without revascularization. Healing proceeds slowly, however, requiring more than a year in many cases. Patients with an ABI <0.5 are more likely to require amputation. Interventions designed to improve outcomes in critical limb ischemia should stratify outcomes based on hemodynamic data and should include a comparative control group given the natural history of ischemic ulcers treated in a dedicated wound program. (J Vasc Surg 2006;44:108-14.)**

Patients presenting with chronic lower extremity ulcers and arterial insufficiency are believed to be at high risk for limb loss.[1] Treatment usually involves an assessment for revascularization, traditionally with surgical bypass or, more recently, using endovascular methods when possible. For those in whom revascularization is not possible or is not warranted, primary amputation may be considered. Numerous authors have documented excellent, long-term limb salvage rates with successful revascularization, particularly with autogenous vein bypass procedures. However, many patients with tissue loss and arterial insufficiency have a limited life expectancy due to coexisting cardiac and other medical conditions.[2,3] For many of these patients, surgical bypass may be risky, with a significant risk of morbidity or mortality. Also, recovery to presurgical levels of function does not occur in all patients.[4,5]

Several methods of percutaneous revascularization have recently been developed for patients not generally believed to be good candidates for endovascular procedures, including those with infrapopliteal lesions and those with extensive femoropopliteal disease. Reports of subintimal recanalization,[6] laser guided angioplasty,[7] and atherectomy devices[8] have described favorable limb salvage in patients with critical limb ischemia (CLI). Given the poor outcome of patients treated with primary limb amputation, associated with a high early mortality and limited ambulatory potential,[9] endovascular procedures are being used with increasing frequency for the treatment of CLI.

Absent from most discussions on the treatment of patients presenting with CLI has been a comparison with the natural history of CLI treated with currently available noninterventional methods. Most physicians working in wound management centers frequently see patients with

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ischemic ulcers who are poor candidates for surgical or endovascular procedures due to medical comorbidity, institutionalized nonambulatory status, or poor outflow vessels in the limb. We have treated patients without extensive tissue loss initially with local wound management and report on the outcome of a cohort of patients with arterial insufficiency and limb ulceration managed nonoperatively. The goal is to provide information on the natural history of this group of patients when they are treated with a dedicated wound management plan.

METHODS

The study was a retrospective review of prospectively collected case series and was approved by the Biomedical Institutional Review Board at the University of North Carolina School of Medicine.

Patients with nonhealing limb ulcers referred to the University of North Carolina Wound Management Center, an outpatient multispecialty wound center, are routinely studied with a noninvasive Doppler evaluation of arterial supply. Ankle and toe pressures are measured, and ankle-brachial indexes (ABI) are calculated. Arterial insufficiency was defined as an ABI index of <0.7 or a toe pressure < 50 mm Hg. *CLI* was defined in accordance with the TransAtlantic Inter-Society Consensus (TASC) recommendations as an ankle pressure < 70 mm Hg or a toe pressure < 40 mm Hg.[10]

Those found to have arterial insufficiency were evaluated by the vascular attending staff for suitability for percutaneous or surgical revascularization. Patients diagnosed with arterial insufficiency and tissue loss who were poor candidates for revascularization were followed prospectively while receiving treatment using the wound management protocol outlined in Table I (online only).

Patients were considered poor candidates for revascularization due to severe medical comorbidity, nonambulatory status, inadequate outflow vessels, or patient/family refusal. Although most patients do not have sufficiently severe medical comorbidity to preclude endovascular revascularization, patients with severe cardiac dysfunction have an increased risk for surgical bypass. Ultimately, this judgement was made in each individual case by the managing vascular specialist.

Early in the time frame studied, patients with long-segment femoral or tibial disease were not treated with endovascular methods. More recently, with the emergence of subintimal recanalization and other techniques, endovascular therapies are used more frequently in this population with a high incidence of diabetes mellitus and its characteristic tibial artery disease. For surgical bypass, tibial and pedal vessels were evaluated with contrast arteriography. Any acceptable vessel > 1 mm with runoff into pedal collaterals was considered acceptable for surgical bypass, including the dorsalis pedis and tarsal arteries.

Wounds were graded using the Wagner scale, which is outlined in Table II (online only).[11] Wounds were included if they measured ≥1 cm in any dimension at the initial evaluation. This protocol is a standard protocol for care of limb ulcers used by many wound healing centers.[12] Each patient with arterial insufficiency and tissue loss was managed primarily by a vascular specialist (W. A. M., M. A. F., R. C. M., B. A. K.). The outlined protocol provided general guidelines for management, but specific treatment decisions were made individually by the treating physician in each case. In addition, active wound healing modalities, including negative pressure therapy, platelet-derived growth factor (PDGF), or bioengineered human skin equivalents, were added in a small number of patients when the treating physician believed they would accelerate wound healing.

Definition of limb ischemia. Limbs were evaluated for arterial supply by measuring ABIs, ankle pressures, toe pressures, and Doppler waveforms. Criteria for study inclusion were an ABI < 0.7 or a toe pressure < 50 mm Hg. Transcutaneous oxygen and laser Doppler measurements were available in a subset of patients but were not numerous enough for statistical analysis.

Definition of chronic wound. Full-thickness ulcers extending through the entire dermis into the subcutaneous tissue present for a minimum of 6 weeks before initiation of treatment were considered to be chronic wounds.

Exclusion criteria. Patients with Wagner grade 4 wounds were excluded from this study if tissue loss was extensive. All Wagner grade 5 wounds were excluded. Patients with necrotizing foot infections were also excluded unless débridement and antibiotic therapy yielded a salvageable foot. In the opinion of the investigators, most of these patients require revascularization to have any chance of limb salvage. Patients with tissue loss that was not deemed salvageable by the treating physician were not included. This included major exposure of the calcaneus or sufficient tendon loss to prohibit useful function of the foot. Patients were excluded if they did not follow-up at the wound management center for at least 6 weeks of treatment, unless follow-up was terminated due to amputation. Because the source of patients for this study was an outpatient clinic, some patients admitted directly to the hospital from other sources with ischemic limb wounds were not included unless follow-up occurred after discharge at the wound center.

End points. The primary end point was the incidence of major limb amputation (below or above knee) 1 year after initiation of treatment. The secondary end point was the incidence of wound closure 1 year after initiation of treatment. Wound closure was defined as complete epithelial coverage with no wound drainage identified at two consecutive clinic visits.

Risk factors associated with an increased incidence of amputation or reduced incidence of wound closure were evaluated, including age, gender, race, history of diabetes mellitus, history of significant renal insufficiency (serum creatinine > 2.5 mg/dL), initial wound grade by Wagner scale, initial wound size, wound location, and severity of ischemia as measured by ABI or toe pressure.

Statistical analysis. Descriptive statistics were expressed as mean ± standard deviation. Satterthwaite un-

Table III. Patient demographic information

Variable	*Percentage*
Age	70.8 ± 14.5 (38–93)*
Gender (male)	58.6
Race	
African American	50.3
White	46.7
Hispanic	3.0
Diabetes mellitus	70.4
Renal insufficiency	27.8
Venous insufficiency	18.3

*Age in years ± standard deviation (range)

equal variance *t* tests were used to evaluate the difference between the means of the respective continuous variables for amputated limbs compared with nonamputated and healed limbs compared with unhealed. Spearman correlations were performed to determine which risk factors were associated with amputation or wound healing. Logistic regression was used to assess the influence of multiple covariates on the outcomes of interest (wound closure and amputation), thereby determining which risk factors were independently associated with these outcomes. For nonordinal variables (wound location) the Mantel Haenszel χ^2 test was used to determine association with outcome. Outcome measures over time are presented using Kaplan-Meier life tables, with significance between groups measured using log-rank analysis.

RESULTS

Between January 1999 and March 2005, 169 limbs in 142 patients satisfied entry criteria to be followed in this protocol. During the same time period, 382 limbs with ischemic ulcerations underwent infrainguinal surgical bypass procedures, and 487 limbs received endovascular procedures for revascularization. Patients did not undergo revascularization because of medical comorbidity (44%), poor functional status (34%), inadequate outflow vessels (14%), or patient/family refusal (8%). Demographic information for the 142 patients is listed in Table III, and initial wound characteristics are listed in Table IV. Outcome information was obtained for 157 limbs at 6 months and 147 limbs at 12 months of treatment.

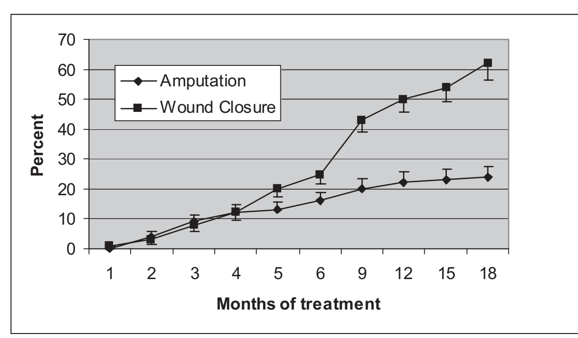
Toe amputations or other foot-sparing surgical procedures were performed during treatment in 28% of limbs. The standard protocol was used initially in all cases. During follow-up treatment, advanced wound therapies were chosen for treatment in 19% of limbs, using PDGF in 12% of limb ulcers, negative pressure therapy in 4%, and bioengineered human skin equivalents in 9%. Combinations of these therapies were used in 6% of ulcers.

The primary end point of below or above knee amputation was reached overall in 37 limbs. At 1 year of follow-up, 52% of limb ulcers were healed and 23% required amputation. Life-table analyses of limb amputation and ulcer closure are presented in Fig 1. Multivariate risk factor analyses revealed that ABI was independently associated

Table IV. Wound characteristics on initial evaluation

	*Limbs (n)**
Wound size, cm² (range)†	8.4 + 20.3 (1-64)
Wound location	
Toe	66
Heel	32
Dorsal foot	21
Plantar foot	12
Ankle	10
Calf area	28
Wound grade (by Wagner scale)	
Grade 1	128
Grade 2	15
Grade 3	14
Grade 4	12
Best ABI (n = 84) (mean)	0.48 ± 0.15
Distribution	
0–0.3	14
0.31–0.5	35
0.51–0.7	35
Toe pressure (n = 85) (mean)	32.7 + 13.0 mm Hg
Distribution	
0-20	19
21-40	39
41-50	27
Number of limbs meeting criteria for CLI	86 (51%)

ABI, Ankle-brachial index; *CLI*, critical limb ischemia.
*Except where noted, data are numbers of limbs.
†Determined by planimetry.

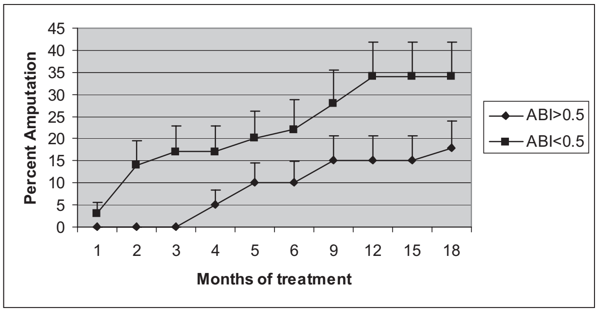


Mos	0	3	6	12	18
#patients	169	169	142	116	109

Fig 1. Limb amputation and wound closure in 169 limbs by life-table analysis. Error bars indicate standard deviation.

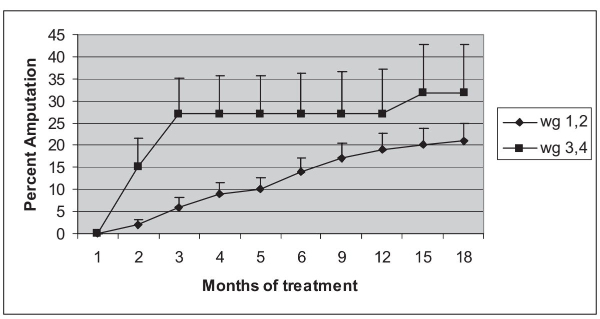
with amputation at 1 year. At 12 months, 32% of limbs with an ABI <0.5 and 43% of limbs with an ABI <0.4 required amputation compared with 15% of limbs with an ABI between 0.5 and 0.7 (P = .01) (Fig 2). Ankle and toe pressures were not predictive of amputation or wound healing.

Eighty-six patients (51%) satisfied the TASC criteria for CLI, and 38% of their limbs required amputation at 12 months. This incidence was significantly more frequent than in the group with subcritical limb ischemia (n = 83, 49%) in whom amputation occurred in 8.5% at 12 months (P = .008 by log-rank testing). The frequency of ulcer healing did not differ significantly between the two groups.



Mos	0	3	6	12	18
#ABI>0.5	51	49	40	33	32
#ABI≤0.5	39	34	31	24	23

Fig 2. Incidence of major amputation in limbs with initial ankle-brachial index *(ABI)* >0.5 compared with limbs with an initial ABI <0.5. *P* = .01 using log-rank analysis. Error bars indicate standard deviation.



Mos	0	3	6	12	18
# wg1,2	143	141	124	102	96
# wg3,4	26	26	18	15	13

Fig 3. Incidence of major amputation in limbs with initial ulcer Wagner grade 1 or 2 compared with initial Wagner grade 3 or 4. *P* = .05 using log-rank analysis. Error bars indicate standard deviation.

Ulcers presenting with wound grade 1 and 2 resulted in amputation less frequently than those with an initial wound grade 3 or 4 by log-rank testing (*P* = .05) (Fig 3). However, an insufficient number of patients with wound grades 2, 3, and 4 were included to allow multivariate analysis of wound grade as an independent predictor of amputation. Categoric values for all variables and their relationship with amputation are listed in Table V. Initial ulcer size was the only risk factor independently associated with ulcer closure at 1 year. Categoric values for variables and their relationship with wound healing are listed in Table VI.

The relationship between wound location and amputation was evaluated using the Mantel-Haenszel test. The data based on location are listed in Table VII. The rate of amputation was higher in the heel, plantar, and dorsal foot but did not reach statistical significance (*P* = .06).

Table V. Risk factors and association with limb amputation

Risk factor	*N*	*Amputated at 18 months, n (%)*	*P*
Gender			.38
Female	70	13 (18.6)	
Male	99	24 (24.2)	
Wound grade			*
1 and 2	143	28 (19.6)	
3 and 4	26	9 (34.6)	
Diabetes mellitus			.15
No	50	8 (16)	
Yes	119	29 (24.4)	
Venous			.78
No	138	31 (22.5)	
Yes	31	6 (19.4)	
Renal insufficiency			.81
No	122	23 (18.9)	
Yes	47	14 (29.8)	
Ankle-Brachial index			.026
>0.5	51	8 (15.7)	
≤0.5	39	12 (30.8)	
Toe pressure (mm Hg)			.16
30 to 50	46	7 (15.2)	
<30	41	9 (22)	

**P* values are from multivariate logistic regression to determine independent association of risk factor with amputation. Wound grade not studied with multivariate analysis.

Table VI. Multivariate analysis of risk factors and association with wound closure

Variable	*N*	*Odds ratio*	*P*
Age	169		.06
Initial wound size	130	−0.244	.003
Ankle-brachial index	90		.18
Treatment time	166		.11
Toe pressure	87		.7

Table VII. Wound location and incidence of amputation

	Amputated (%)	*Not amputated (%)*	*Total*
Toe	12 (18.2)	54 (81.8)	66
Plantar foot	4 (7.3)	8 (14.7)	12
Dorsal foot	7 (33.30)	14 (66.7)	21
Heel	11 (34.4)	21 (65.6)	32
Ankle	1 (10.0)	9 (90.0)	10
Leg	2 (7.1)	26 (92.0)	28
Total	37	132	169

DISCUSSION

In a recent editorial for the *Journal of Vascular Surgery*, Nehler, Hiatt, and Taylor noted that our understanding of the natural history of CLI is limited and that the current approach to CLI is excessively lesion-focused and inadequately patient-focused. They suggest that in some cases, early amputation may be preferential to aggressive attempts at revascularization. However, data are currently lacking to determine which patients should definitively be treated with early amputation.[13]

Numerous recent studies have described methods for treatment of specific types of arterial obstruction for CLI, reporting success with high limb-salvage rates. Kudo et al[14] reported that although primary patency for 138 limbs treated with CLI using percutaneous transluminal angioplasty was only 31%, secondary patency was achieved in 80% and limb salvage in 89%. They concluded that PTA is an effective procedure for the treatment of CLI. Using excimer laser assisted angioplasty (LACI), Bosiers et al[7] treated 51 limbs with CLI, with a primary end point of limb salvage. The rate of limb salvage at 6 months was 90.5%, prompting the authors to recommend LACI for treatment of accessible lesions in patients with CLI.[7]

Similar reports have recently been published describing angioplasty and/or stenting,[15] excisional atherectomy devices,[16] and subintimal recanalization,[17] all with good initial success and favorable limb salvage results. Unfortunately, none of these studies adhered to the hemodynamic criteria for CLI outlined by the TASC, including only patients with an ankle pressure <70 mm Hg or a toe pressure <40 mm Hg.[7,14-17] In some studies, preprocedure ankle pressures and ABIs were not reported, and in the remainder, the average preintervention ABI was 0.4 to 0.54. It is likely that a significant number of limbs with ankle pressures >70 were included. Patients with an ABI >0.5 are probably not at high risk for limb loss, so an outcome measuring limb salvage in these patients is less meaningful.

Similarly for surgical bypass, although a successful revascularization yields a high rate of patency and limb salvage at 5 years, significant morbidity and occasional mortality are associated with the procedure.[4,5] Some patients are poor candidates due to medical comorbidity or unsuitable lower limb outflow vessels. Attempts at surgical revascularization are not warranted if a patient group can be defined with a high probability of healing without revascularization. Unfortunately, neither studies of percutaneous nor surgical revascularization have included patient groups treated without revascularization for outcome comparison.

The goal of this study was to provide outcome information from a cohort of patients with arterial insufficiency and tissue loss treated without intervention. Approximately half of the limbs in this study satisfied the hemodynamic criteria for CLI outlined by the TASC. The rest had less severe arterial insufficiency and were included to provide outcome information on this patient group also.

Patients were identified in an outpatient clinic, so patients with acute, infected, or rapidly worsening ischemic wounds that would typically present to an emergency department and require hospital admission may not have been included. Many patients were institutionalized and nonambulatory and might have been better treated with primary amputation; however, families are often reluctant to consent to amputation. In these cases, we used wound treatment protocols to attempt to generate healing or at least maintain a wound in a stable, uncomplicated condition for palliation.

Patients with extensive, complex wounds and those with necrotizing infections were rarely treated without revascularization. This, along with the patient recruitment source, resulted in the low incidence of Wagner grade 3 and 4 wounds in this study. Ulcer size, however, was not a limitation, as the average size was >8 cm^2, with ulcers as large as 64 cm^2 included. For these reasons, we believe this study describes the natural history of a segment of patients with arterial insufficiency and tissue loss, particularly those with noncomplicated ulcers.

The primary outcome revealed that most patients did not require amputation, even those with more severe arterial insufficiency; however, ulcer closure was slow, with only 25% closed at 6 months and just over 50% closed at a year. In limbs where hemodynamic criteria were consistent with CLI (as defined in *Methods*), the incidence of limb loss was high—over a third at 1 year—so revascularization should be performed whenever possible, but not so high that we would recommend primary amputation on a routine basis. In fact, we believe these data argue that patients who cannot undergo revascularization should have a trial of careful wound management before primary amputation, even in those who are functionally impaired.

Several studies of pharmacologic therapies for CLI have provided data on the natural history of patients with limb-threatening ischemia. Three prospective placebo-controlled studies that evaluated the use of iloprost for CLI reported an average 39% incidence of limb loss in the control groups treated without study medication,[18-20] a rate similar to the patient group in this study with hemodynamic criteria consistent with CLI.

Previous studies of limb loss in patients with limb ulcers have defined diabetes mellitus and renal insufficiency as risk factors associated with amputation. We did not identify these as risk factors, but this may be related to an inadequate patient sample size (47 patients with renal insufficiency, 50 patients without diabetes mellitus). The incidence of limb loss for patients with renal insufficiency was 29.8% compared with 18.9% for those without renal insufficiency, but this difference did not reach statistical significance.

Wound care using the protocol outlined in Table I (online only) is labor intensive, expensive, and often requires the patient to significantly limit activity levels. This method of management would not be desirable for most ambulatory patients if revascularization were feasible without excessive risk. Successful revascularization would likely result in more rapid healing and a more rapid return to activity. Despite the effort required for 6 to 12 months of outpatient wound management, we believe this is preferable to primary amputation for most patients.

In the group of patients who had hemodynamic criteria consistent with subcritical stenosis, limb loss was less common. These patients should not typically be included in critical limb ischemia studies in which limb salvage is a primary outcome unless a placebo group is included for comparison.

We reviewed the ability of noninvasive Doppler studies to predict the probability of limb loss. Although an ABI of <0.5 was a significant predictor for limb loss, valid ABIs were obtainable in just over half of the limbs studied due to the high incidence of severe diabetes mellitus with noncompressible vessels. Unfortunately, neither ankle nor toe pressures were predictive of limb loss or wound closure in this patient population.

Other methods have been described to assist in predicting the potential for wound healing, including transcutaneous pO_2[21,22] and laser Doppler scans.[23] Although we currently use these methods, they were not available throughout the study, and insufficient data were generated to evaluate their predictive potential. Noninvasive methods with a high sensitivity and specificity for predicting healing without revascularization would greatly assist in patient management.

Based on the results from this study, we believe that patients should be considered for primary amputation when the ABI is <0.5, with no potential for revascularization and with extensive tissue loss. Although we could not confirm that advanced wound grade is an independent predictor of limb loss, it is likely that the study of a larger group of patients would confirm this association. If tissue loss is not extensive, initial care with a protocol similar to that outlined in Table I (online only) may be recommended and limb salvage expected in most patients.

The role for advanced wound-healing modalities such as growth factors and bioengineered human skin equivalents is unclear at this time. Less than one fourth of patients were treated with these techniques in a nonrandomized fashion, so their impact on healing is difficult to assess. Current clinical trials evaluating newer growth factors are actively enrolling patients with CLI and, it is hoped, will yield therapies to assist in the treatment of these patients when invasive procedures are not desirable.

CONCLUSION

In this study of a subset of patients with arterial insufficiency and uncomplicated, stable limb ulcers treated without revascularization, major amputation was necessary in 23% of limbs at 12 months. Wound healing was slow but eventually achieved in 52% at 12 months. We believe these are acceptable outcomes for poor candidates for surgical or endovascular intervention, so primary amputation should not usually be considered in this patient group. Better strategies for prediction of wound healing are needed because ABI and toe pressures are not useful for a large percentage of patients. We believe that studies involving interventions aimed at the treatment of CLI should include only patients with severe hemodynamic arterial insufficiency as defined by the TASC, because the patients with subcritical ischemia and tissue loss enrolled in this study had a relatively low risk of limb loss without revascularization.

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AUTHOR CONTRIBUTIONS

Conception and design: WAM, SWD, MAF, RCM, JJF, BAK
Analysis and interpretation: WAM, SWD, BA, MAF, RCM, JJF
Data collection: WAM, SWD, RCM, JJF
Writing the article: WAM, SWD
Critical revision of the article: WAM, BA, MAF, RCM, JJF, BAK
Final approval of the article: WAM, SWD, BA, MAF, RCM, JJF, BAK
Statistical analysis: WAM, SWD, BA
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Overall responsibility: WAM

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Table I (online only). Protocol for management of limb ulcers associated with arterial insufficiency

Outpatient visit frequency weekly over first 4 weeks, then every 1 to 3 weeks
Wound documentation
Digital photography
Wound planimetry to determine wound area
Determination of wound grade by Wagner scale
Débridement
Sharp surgical removal of nonviable tissue and surrounding callus at each visit if necessary
Thick eschar removed only when separating at wound edges
Pressure offloading
Podiatry-directed use of appropriate offloading device based on wound location
Infection management
Topical agents rarely used
Débridement, deep culture, systemic antibiotics if increasing bioburden or infection is suspected clinically
Topical agents
Dressing products chosen to maintain moist wound bed, most often hydrogel/gauze or absorbent foam dressings

Table II (online only). Wagner grading scale for leg and foot ulcers

Grade 0
Preulcerative lesion, healed ulcers, bony deformity
Grade 1
Superficial ulcer, no subcutaneous tissue exposure
Grade 2
Penetration through the subcutaneous tissue (may expose bone, tendon, ligament, joint)
Grade 3
Osteitis, abscess, osteomyelitis
Grade 4
Gangrene of forefoot
Grade 5
Gangrene of entire foot